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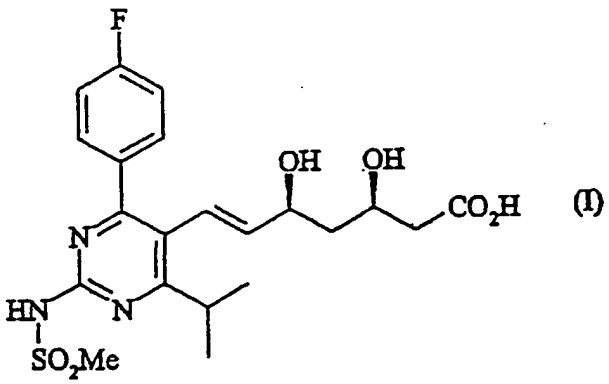
(54) Title: (E)-7(4-FLUOROPHENYL)-6ISOPROPYL2-MESYLAMINOPYRIMIDIN-5-Y)-(3R,5S)-DIHYDROXY-HEPT-6-ENOIC ACID.



(I)

(57) Abstract: The present invention relates to the compound of formula (I): or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof. This compound of formula (I) is conveniently called: (E)-7[4-(4-fluorophenyl)-6-isopropyl-2-mesylaminopyrimidin-5-yl]-(3R,5S)-dihydroxyhept-6-enoic acid.

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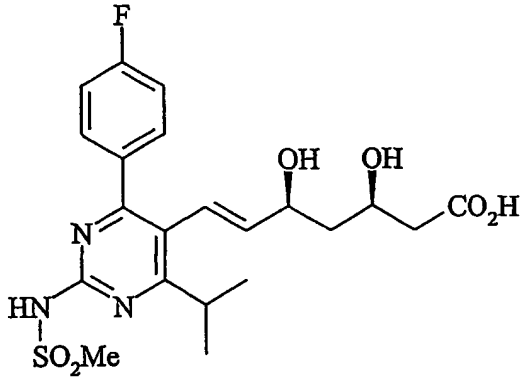
(E)-7(4-(4-FLUOROPHENYL)-6ISOPROPYL2-MESYLAMINOPYRIMIDIN-5-YL)-(3R,5S)-DIHYDROXYHEPT-6-ENOIC ACID

The present invention relates to a pyrimidyldihydroxyheptenoic acid derivative which is an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, its salts, processes for its preparation and its use in medicaments.

The first generation of drugs for the treatment of atherosclerosis by inhibiting the activity of HMG-CoA reductase, are mevinolin (US 4,231,938), pravastatin sodium (US 4,346,227) and simvastatin (US 4,444,784) which are fungal metabolites or chemical derivatives thereof. More recently a wide variety of synthetic inhibitors of HMG-CoA reductase have been disclosed including certain pyrimidyldihydroxyheptenoic acid derivatives (such as those disclosed in EP 521,471).

We have surprisingly found that a particular pyrimidyldihydroxyheptenoic acid derivative is a potent inhibitor of HMG-CoA reductase, which plays a major role in the synthesis of cholesterol, and thus it may suppress the biosynthesis of cholesterol. This compound is therefore potentially useful in the treatment of hypercholesterolemia, hyperlipoproteinemia and atherosclerosis and other disease conditions mediated by HMG-CoA reductase.

The present invention relates to the compound of formula (I):



(I)

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

This compound of formula (I) is conveniently called:
(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-mesylaminopyrimidin-5-yl]-(3R,5S)-dihydroxyhept-6-enoic acid.

Suitable pharmaceutically acceptable salts include base salts such as an alkali metal salt for example sodium; an alkaline earth metal salt for example calcium or magnesium; an ammonium salt; or an organic amine salt such as an alkylamine for example methylamine, ethylamine, diethanolamine, tris(hydroxymethyl)methylamine, benzylamine, 4-methoxybenzylamine, triethylamine, morpholine, *N*-methylpiperidine, *N*-ethylpiperidine, procaine, dibenzylamine, *N,N*-dibenzylethylamine or amino acids for example lysine. There may be more than one cation or anion depending on the number of charged functions and the valency of the cations or anions. Preferred pharmaceutically acceptable salts are the sodium salt and the calcium salt. In one aspect of the invention the preferred salt is the sodium salt. In another aspect of the invention the preferred salt is the calcium salt.

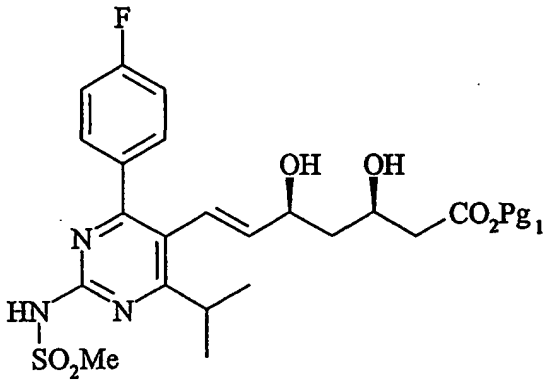
The compound of formula (I) may be administered in the form of an *in vivo* hydrolysable ester. This is an ester which is broken down in the human or animal body to give the compound of the formula (I). Examples of *in vivo* hydrolysable esters of the compound of the formula (I) are, for example, C_{1-6}alkoxymethyl esters for example methoxymethyl; C_{1-6}alkanoyloxymethyl esters for example pivaloyloxymethyl; phthalidyl esters; C_{3-8}cycloalkoxycarbonyloxyC_{1-6}alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl; phosphate esters; α-acyloxyalkyl ethers for example acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy; alkanoyl esters for example benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl; alkoxycarbonyl (to give alkyl carbonate esters); dialkylcarbamoyl and *N*-(dialkylaminoethyl)-*N*-alkylcarbamoyl (to give carbamates); dialkylaminoacetyl and carboxyacetyl. Examples of substituents on benzoyl include morpholino and piperazino linked from a ring nitrogen atom via a methylene group to the 3- or 4- position of the benzoyl ring. For the avoidance of doubt, an *in vivo* hydrolysable ester of the compound of formula (I) also includes the compound of formula (I) in a lactonised (i.e. cyclic ester) form.

A preferred aspect of the invention relates to the compound of formula (I) and pharmaceutically acceptable salts thereof.

It is also to be understood that the compound of formula (I) may exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms.

In another aspect the present invention provides a process for preparing the compound of formula (I) or a pharmaceutically acceptable salt thereof which process comprises:

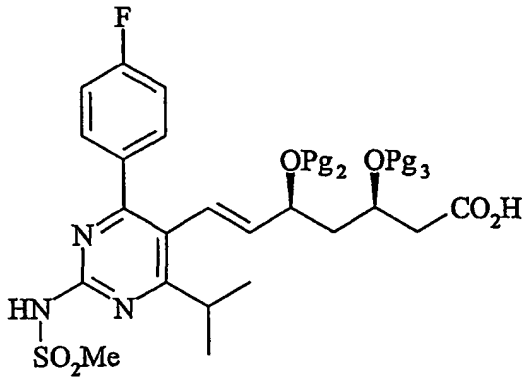
i) deprotecting a compound of formula (II):



(II)

wherein Pg_1 is an acid protecting group; or

ii) deprotecting a compound of formula (III):



(III)

wherein Pg_2 and Pg_3 are alcohol protecting groups or Pg_2 and Pg_3 together form a cyclic alcohol protecting group;

and thereafter if required:

forming a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

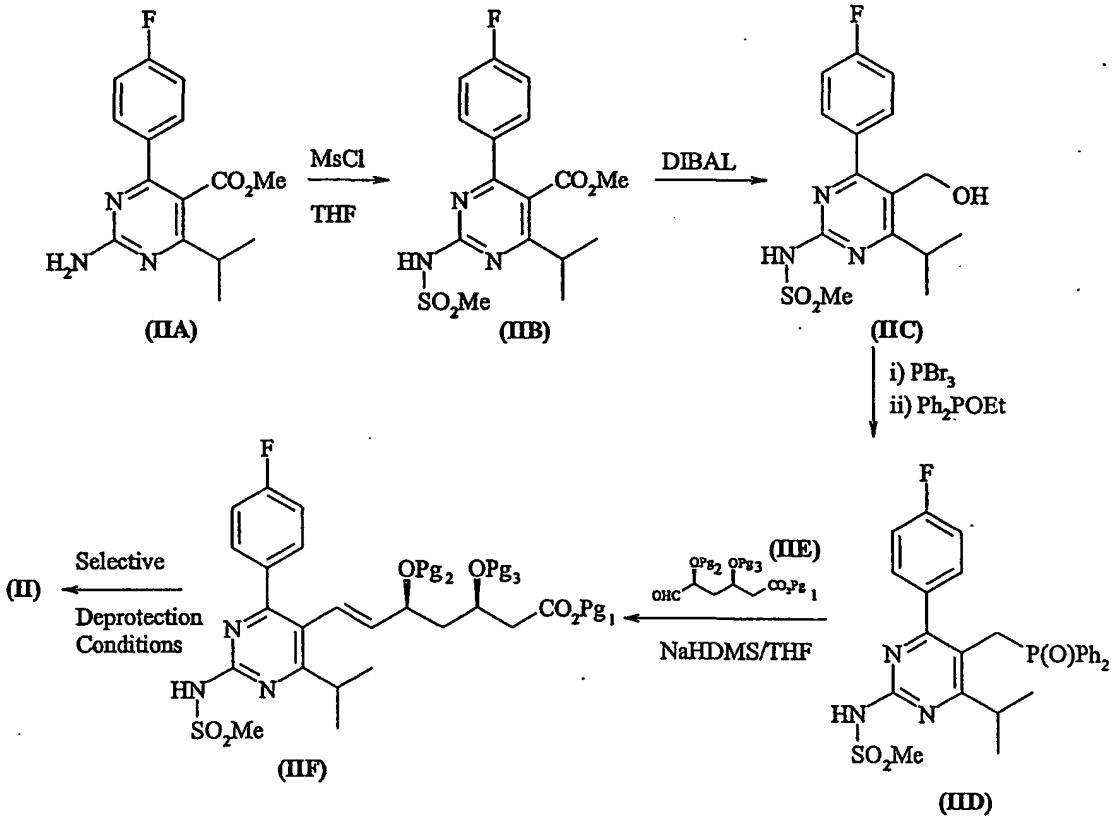
Specific reaction conditions for the above reactions are as follows:

Process i) A suitable value for Pg_1 is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by

treatment with an acid, for example an organic acid such as trifluoroacetic acid or treatment with an alkali, for example sodium hydroxide, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

Compounds of formula (II) may be prepared according to the following scheme.

Scheme 1.



The selective deprotection conditions are those in which Pg_2 and Pg_3 are removed, but not Pg_1.

Compounds of formula (IIA) and (IIE) are known compounds or they are prepared from known compounds by standard conditions known in the art.

Process ii) Suitable values for Pg_2 and Pg_3 are, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by

hydrogenation over a catalyst such as palladium-on-carbon. Where Pg_2 and Pg_3 together form a cyclic alcohol protecting group a suitable value is for example a dimethyl methylene group. This may be removed by treatment with a suitable acid, for example hydrochloric acid.

Compounds of formula (III) may be prepared according to Scheme 1, but wherein the selective deprotection conditions are chosen such that Pg_1 is removed and Pg_2 and Pg_3 remain in place.

In order to use the compound of formula (I) or a pharmaceutically acceptable salt thereof for the therapeutic treatment (including prophylactic treatment) of mammals including humans, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

The pharmaceutical compositions of the compound of this invention may be administered in standard manner for the disease condition that it is desired to treat, for example by oral, topical, parenteral, buccal, nasal, vaginal or rectal administration or by inhalation. For these purposes the compound may be formulated by means known in the art into the form of, for example, tablets, capsules, aqueous or oily solutions, suspensions, emulsions, creams, ointments, gels, nasal sprays, suppositories, finely divided powders or aerosols for inhalation, and for parenteral use (including intravenous, intramuscular or infusion) sterile aqueous or oily solutions or suspensions or sterile emulsions. A preferred route of administration is oral.

In addition to the compound the pharmaceutical composition of this invention may also contain, or be co-administered (simultaneously or sequentially) with, one or more pharmacological agents of value in treating one or more disease conditions referred to hereinabove.

The pharmaceutical compositions of this invention will normally be administered to humans so that, for example, a daily dose of 0.5 to 200 mg (and preferably of 0.1 to 100 mg for oral administration) is received. This daily dose may be given in divided doses as necessary, the precise amount of the compound received and the route of administration depending on the weight, age and sex of the patient being treated and on the particular disease condition being treated according to principles known in the art.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises the compound of formula (I) as defined hereinbefore or a

pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided the compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined hereinbefore for use in a method of treatment of the human or animal body by therapy.

A further feature of the present invention is the compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a medicament.

Conveniently this is the compound of formula (I), or a pharmaceutically acceptable salt thereof, for use as a medicament to inhibit HMG-CoA reductase, in a warm-blooded animal such as a human being.

Thus according to a further aspect of the invention there is provided the use of the compound of the formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the inhibition of HMG-CoA reductase in a warm-blooded animal such as a human being.

According to a further feature of the invention there is provided a method of inhibiting HMG-CoA reductase in a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of the compound of formula (I) or a pharmaceutically acceptable salt thereof.

According to a further feature of the invention there is provided the compound of formula (I) or a pharmaceutically acceptable salt thereof in isolated form.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises the compound formula (I) or a pharmaceutically acceptable salt thereof in isolated form, in association with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided the compound of formula (I) or a pharmaceutically acceptable salt thereof in isolated form, for use in a method of treatment of the human or animal body by therapy.

A further feature of the present invention is the compound of formula (I) or a pharmaceutically acceptable salt thereof in isolated form, for use as a medicament.

Conveniently this is the compound of formula (I) or a pharmaceutically acceptable salt thereof in isolated form, for use as a medicament to inhibit HMG-CoA reductase in a warm-blooded animal such as a human being.

Thus according to a further aspect of the invention there is provided the use of the compound of formula (I) or a pharmaceutically acceptable salt thereof in isolated form, in the manufacture of a medicament for use in the inhibition of HMG-CoA reductase in a warm-blooded animal such as a human being.

According to a further feature of the invention there is provided a method of inhibiting HMG-CoA reductase in a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of the compound of formula (I) in isolated form or a pharmaceutically acceptable salt thereof.

Particularly the inhibition of HMG-CoA reductase refers to the treatment of hypercholesterolemia, hyperlipoproteinemia or atherosclerosis.

The term "isolated form" as used herein means that the compound is produced and purified synthetically.

The following Biological Test Methods serve to illustrate the present invention.

Test (a) - Rat liver microsomes

Liver microsomes were prepared from normal fed rats by a standard method.

The assay method was a modification of the method described by Kuroda & Endo (Biochimica et Biophysica Acta 486 (1977) 70-81).

The reaction mixture contained in a total volume of 50µl : 100mM potassium phosphate buffer pH 7.4, 100µM DL-[3-^{14}C]-HMGCoA, 5mM NADPH, 10mM EDTA, 10mM DTT, and 50µg microsomal protein. The compound of formula (I) at various concentrations was added in 5µl of 50% DMSO. The reaction was started by addition of the microsomes and the mixture incubated at 37°C for 30 minutes. After termination of the reaction by addition of 10µl 2M HCl the mixture was incubated at 37°C for 15 min to lactonize the product then applied to a silica gel TLC plate (Whatman LK5D). Chromatograms were developed in toluene:acetone 1:1 and the spots corresponding to products visualized with iodine vapour. Spots corresponding to mevalonolactone were scraped and radioactivity measured in a liquid scintillation counter. Seven-point dose response curves were constructed and the data analysed to determine IC_{50} values using a curve fitting programme (Origin, Microcal Software Inc).

Test (b) - Human HMGCoA reductase catalytic domain

A soluble catalytic fragment of human HMGCoA reductase containing residues 419 - 888 was expressed in E coli and purified by affinity chromatography.

The assay method was a modification of the method described by Louis-Flamberg *et al* (Biochemistry 29 (1990) 4115-4120).

The reaction mixture contained in a total volume of 1ml : 100mM MOPS buffer pH 7.2, 200mM NaCl, 100mM KCl, 1mM EDTA, 10mM DTT, 100μM HMGCoA, 250μM NADPH, and 5nM enzyme. The compound of formula **(I)** at various concentrations was added in 100μl of 50% DMSO. The reaction was started by addition of the enzyme and the mixture incubated at 25°C for up to 20 minutes. HMGCoA reductase activity was assayed continuously by monitoring the decrease in absorbance at 340nm due to NADPH oxidation in a spectrophotometer (Perkin-Elmer Lambda Bio 40). Data was analysed according to the method of Morrison & Walsh (Advanc. Enzymol. 61 (1988) 201-301) in order to determine IC_{50} values for both initial and steady state rates, using non-linear least squares fitting with Grafit 4.0 software (Erithacus Software 1998).

Example

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

(i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25°C;

(ii) organic solutions were dried over anhydrous magnesium sulphate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30mmHg) with a bath temperature of up to 60°C;

(iii) chromatography means flash chromatography on silica gel (Merck Keiselgel ART 9385); thin layer chromatography (TLC) was carried out on silica gel plates; where a "silica Mega Bond Elut" column is referred to, this means a column containing 10g of silica of 40 micron particle size, the silica being contained in a 60ml disposable syringe and supported by a porous disc, obtained from Varian, Harbor City, California, USA under the name "Mega Bond Elut SI"; where a "Bond Elut" column is referred to, this means a column containing 10g of C-18 silica, the silica being contained in a 60ml disposable syringe and supported by a porous

disc of 54Å pore size, obtained from International Sorbent Technology under the name "ISOLUTE"; "ISOLUTE" is a registered trade mark;

(iv) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;

(v) yields are given for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;

(vi) when given, NMR data is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300 MHz; s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet; br, broad;

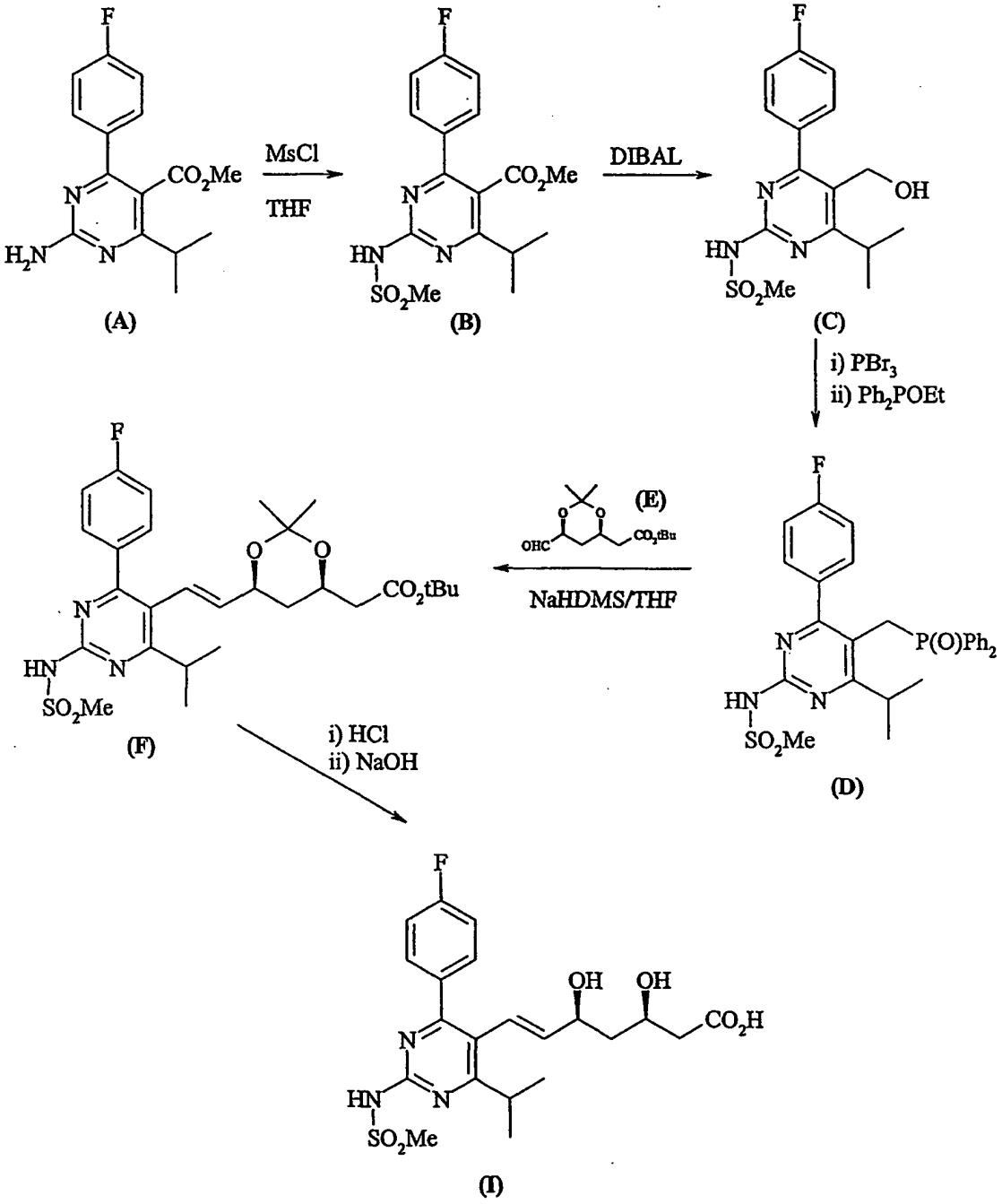
(vii) mass spectra were obtained using a caesium fast ion bombardment ionisation source in positive ion mode at 10keV in a 3-nitrobenzylalcohol matrix; values for m/z are given; generally, only ions which indicate the parent mass are reported; and

(viii) the following abbreviation has been used:

THF tetrahydrofuran.

The compound of formula (I) may be prepared according to the following scheme:

Scheme 2.


F
CO2Me
N
H2N
N
(A)
MsCl
THF
HN
SO2Me
(B)
DIBAL
OH
(C)
i) PBr3
ii) Ph2POEt
P(O)Ph2
(D)
(E)
OHC
CO2tBu
NaHDMS/THF
CO2tBu
(F)
i) HCl
ii) NaOH
OH
CO2H
(I)

Example 1

Compound of formula (I)

Compound F (Method 4; 200mg) was dissolved in acetonitrile (5ml) under nitrogen. The reaction mixture was heated to 35°C and then hydrochloric acid (0.535ml, 1M solution) was added dropwise. The reaction mixture was heated at 35°C for 3 hours and then cooled to 25°C over 30mins. Sodium hydroxide (1.07ml, 1M solution) was added dropwise until the solution became pH 12. The solution was stirred at room temperature and then additional sodium hydroxide (0.3ml, 1M) was added and the pH increased to 13.25. The mixture was stirred at room temperature for a further 30mins and then stored in a refrigerator overnight. The aqueous phase was freeze dried for 6 hours to yield a solid (0.1754g). The solid was purified by solid phase extraction. The solid was dissolved in an mixture of ethyl acetate and methanol (1:1) and loaded onto a 10g silica Mega Bond Elut column. The material was eluted with ethyl acetate (50ml) and ethyl acetate : ethanol; 8 : 2 (50 x 5 ml) to yield a colourless oil with traces of solid (77mg). A C-18 Bond Elut cartridge (10g) was preconditioned with acetonitrile (30ml) and formic acid (0.01M) (30ml) and the oil was purified on the Bond Elut column eluting with acetonitrile : formic acid (0.01M); 2 : 8 increasing to 4 : 6 to yield an oil (54.4mg). NMR 1.2 (d, 6H), 1.35 (m, 1H), 1.5 (m, 1H), 2.2 (dd, 1H), 2.3 (dd, 1H), 3.4 (s + m, 4H), 3.85 (m, 1H), 4.15 (m, 1H), 4.85 (brs, 1H), 5.6 (dd, 1H), 6.45 (dd, 1H), 7.25 (t, 2H), 7.65 (m, 2H); m/z 468 (MH^+).

Preparation of Starting Materials

The starting materials for the Example above are either commercially available or are readily prepared by standard methods from known materials. For example the following reactions are illustrations but not limitations of the preparation of some of the starting materials used in the above reactions.

Method 1

Compound B

Sodium t-pentoxide (0.4420g) and dimethoxyethane (5ml) were added to Compound A (JP 06256318; 0.5007g) under argon and the mixture was stirred at room temperature for 30mins, before cooling to -10°C. Methane sulphonyl chloride (0.22ml) was added dropwise

and the reaction was stirred at -10°C for a further 20mins before water was added (3.5ml). The organic layer was separated and evaporated to dryness to yield a pale yellow residue. This was purified by column chromatography eluting with petrol : ethyl acetate; 90 : 10 increasing to 85 : 15 to give a white solid (0.5217g, 82%). NMR ($CDCl_3$): 1.25 (d, 6H), 3.10 (m, 1H), 3.42 (s, 3H), 3.65 (s, 3H), 7.1 (t, 2H), 7.5 (brs, 1H), 7.6 (m, 2H); m/z 368 (MH^+).

Method 2

Compound C

Toluene (0.6ml) was added to Compound B (Method 1; 135mg) under argon and the suspension was cooled to -10°C. Diisobutylaluminium hydride (0.85ml of a 1.5M solution in toluene) was added and the resulting yellow suspension was stirred at -10°C for a further hour. Methanol (10µl) was added and the reaction mixture was allowed to warm to room temperature. In a separate flask, concentrated hydrochloric acid (0.25ml) and water (0.45ml) were mixed and heated to 40°C. The reaction mixture was added dropwise to the acid solution and the resulting solution was heated at 40°C for 20mins before allowing to cool to room temperature. The organic layer was separated and evaporated to dryness to yield a yellow oil. This was purified by column chromatography eluting with petrol : ethyl acetate; 80 : 20 increasing to 70 : 30 to give a colourless oil (102mg). M/z 340 (MH^+).

Method 3

Compound D

Dry dichloromethane (15ml) was added to Compound C (Method 2; 1.2328g) under argon and the mixture was stirred for 30mins. Phosphorous tribromide (173µl) was added and the mixture was stirred at room temperature for 1hour. Water (30ml) was added and the organic layer was separated. The aqueous layer was re-extracted with dichloromethane (15ml) and the combined organic layers were dried and evaporated to dryness to give a white solid. The white solid was dissolved in dry toluene (28ml) under argon and the mixture was heated to 60°C. Ethyl diphenylphosphinite (1.18ml) was added and the mixture was heated at 60°C for 3 hours during which time a white solid precipitated out of the solution. The reaction mixture was stored in a refrigerator for 48hours and then filtered. The resulting solid was

washed with toluene and dried (1.625g, 85%). NMR (DMSO-d_6): 1.1 (d, 6H), 3.2 (m, 1H), 3.35 (s, 3H), 3.95 (d, 2H), 7.0-7.3 (m, 6H), 7.4 (m, 4H), 7.55 (m, 6H); m/z 524 (MH^+).

Method 4

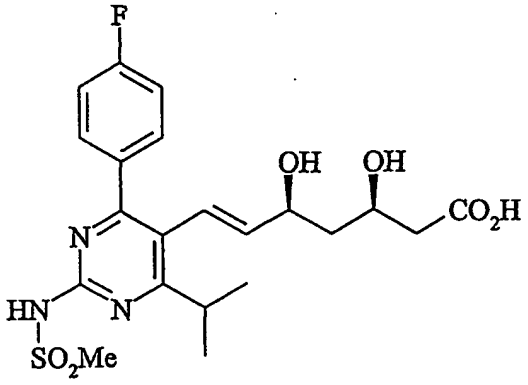
Compound F

Compound D (Method 3; 1.5033g) was dissolved in dry THF (22ml) under argon and the solution was cooled to -60°C. Sodium hexamethyldisilazane (5.7ml of a 1M solution in THF) was added dropwise and the reaction was stirred at -60°C for 20mins. Compound E (EP 319847, 5.72ml of 16.4% w/w solution in toluene) was added dropwise and the reaction was stirred at -60°C for 15mins and then allowed to warm up gradually to 10°C. Water (1.5ml) was added followed by glacial acetic acid (0.5ml) and the temperature was increased to 25°C. The mixture was stirred at ambient temperature for 15mins and then the THF was removed by evaporation. Additional water (5ml) and toluene (2ml) were added and the organic layer was separated and washed with saturated sodium hydrogen carbonate solution (5ml) and water (5ml). The aqueous layers were re-extracted with ethyl acetate (5ml) and the combined organic layers were evaporated to dryness to yield an oil which solidified on standing. The residue was pre absorbed onto silica by dissolving in methanol and then purified by column chromatography eluting with isohexane : ethyl acetate; 8 : 2 to yield a yellow oil (1.088g, 67.5%). NMR (DMSO-d_6): 1.2 (d, 6H), 1.49 (s, 9H), 2.21 (dd, 2H), 2.39 (dd, 2H), 3.3 (s, 3H +m, 1H), 3.35 (s, 6H), 4.22 (m, 1H), 4.52 (m, 1H), 5.41 (dd, 1H), 6.52 (d, 1H), 7.25 (t, 2H), 7.6 (m, 2H), 11.25 (brs, 1H); m/z 564 (MH^+).

Claims:

What we claim is:-

1. The compound of formula (I)



(I)

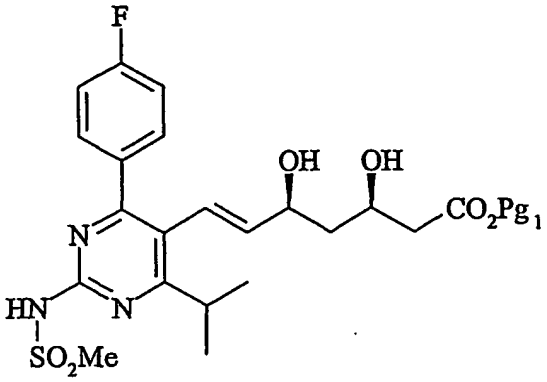
or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

2. The compound as claimed in claim 1 in the form of an alkali metal salt, an alkaline earth metal salt, an ammonium salt or an organic amine salt.

3. The compound as claimed in claim 1 or 2 in the form of a sodium or calcium salt.

4. A process for preparing the compound of formula (I) as claimed in claim 1, or a pharmaceutically acceptable salt thereof or an *in vivo* hydrolysable ester thereof, which process comprises:

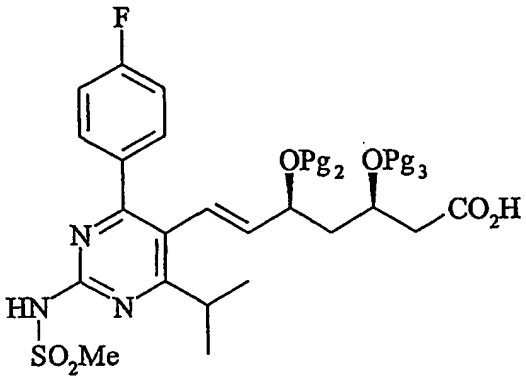
i) deprotecting a compound of formula (II)



(II)

wherein Pg_1 is an acid protecting group; or

ii) deprotecting a compound of formula (III)



(III)

wherein Pg_2 and Pg_3 are alcohol protecting groups or Pg_2 and Pg_3 together form a cyclic alcohol protecting group;

and thereafter if required:

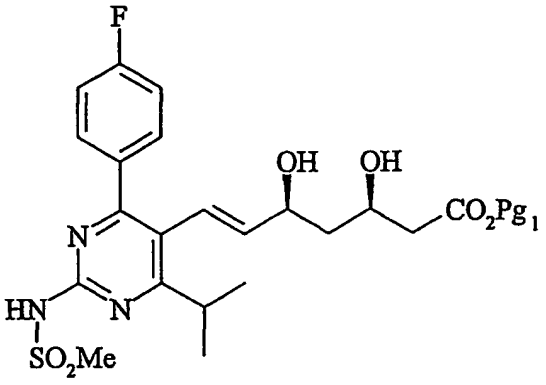
forming a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

5. A pharmaceutical composition which comprises the compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt thereof or an *in vivo* hydrolysable ester thereof, in association with a pharmaceutically acceptable excipient or carrier.

6. The compound of formula I as defined in claim 1, or a pharmaceutically acceptable salt thereof or an *in vivo* hydrolysable ester thereof, for use in a method of treatment of the human or animal body by therapy.

7. The use of the compound of formula I as defined in claim 1, or a pharmaceutically acceptable salt thereof or an *in vivo* hydrolysable ester thereof, in the manufacture of a medicament for use in the inhibition of HMG-CoA reductase in a warm-blooded animal.

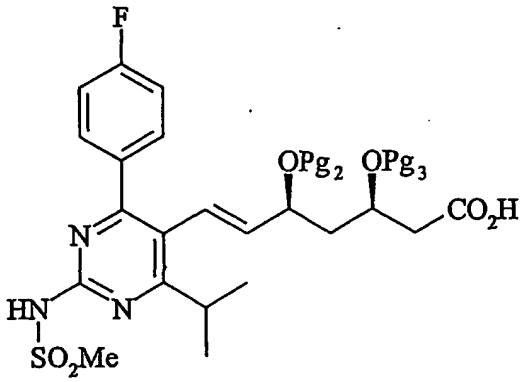
8. A compound of the formula (II)



(II)

wherein Pg_1 is an acid protecting group.

9. A compound of the formula (III)



(III)

wherein Pg_2 and Pg_3 are alcohol protecting groups or Pg_2 and Pg_3 together form a cyclic alcohol protecting group.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 01/01979

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D239/42 A61K31/505 A61P3/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 521 471 A (SHIONOGI & CO) 7 January 1993 (1993-01-07) cited in the application claims 1,5; example 1	1-10
Y	EP 0 547 000 A (SANDOZ LTD) 16 June 1993 (1993-06-16) claims; examples	1-10
Y	MASAMICHI WATANABE ET AL.: "synthesis and biol. activity of Methanesulfonamide Pyrimidine-substituted 3,5-dihydroxy-6-heptanoates as HMG-CoA reductase inhibitors" BIOORG. & MED. CHEMISTRY, vol. 5, no. 2, 1997, pages 437-444, XP000882043 example 3A	1-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 July 2001	07/08/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Menegaki, F

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INTERNATIONAL SEARCH REPORT

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